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IMPACT OF RACIAL GENETIC POLYMORPHISM ON THE PROBABILITY OF FINDING AN HLA-MATCHED DONOR[1]

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As successful organ or marrow transplantation correlates with the degree of HLA-compatibility between patient and donor, registries have been developed to facilitate matching. However, racial minority groups have a lower chance of finding a match. We evaluate the impact of the biology of racial genetic polymorphism upon the probability of finding an HLA match for patients of different racial groups. The National Marrow Donor Program has compiled the HLA types of 20,449 patients and 1,625,159 potential volunteer donors. These HLA types were used to estimate the probability of finding an HLA-matched donor for patients of different racial groups. We estimated the HLA haplotype frequencies for different races, and then determined the probability of finding matched donors, given several hypothetical registry sizes. We confirmed that patients of minority races searching the current National Marrow Donor Program registry have low probabilities of finding matches. This was only partly due to the smaller number of donors from these racial minorities, as the observation persisted even when hypothetical donor registry sizes were the same for all racial groups. We demonstrate that African-Americans are more polymorphic with respect to HLA, and are hence less likely to find donors at any given registry size. An increase in the recruitment of minority racial groups for organ and marrow donors will only partially alleviate the problem of equal access to HLA matches for patients belonging to racial minority groups. It will therefore be important to attempt to improve methods for transplantation using HLA-mismatched donors.

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During the last three decades, transplantation of bone marrow, kidney, and more recently heart, liver, lung and pancreas has become the standard of care for the treatment of many otherwise fatal diseases (*1–5*). For marrow and kidney transplant patients, the ideal donor is a sibling who by chance has inherited the same two human leukocyte antigen (HLA)* haplotypes from the parents. However, given current family sizes, the average probability of having such a donor is less than 30% (*6*). As a result, transplant physicians have turned to utilization of unrelated donors. For patients receiving transplants either from related or unrelated donors, the closer the HLA match, the greater the likelihood of success (*7–9*). This observation has led to the establishment of two systems, the United Network for Organ Sharing (UNOS) for solid organs, and the National Marrow Donor Program (NMDP) for marrow donors, both of whose goals are to maximize the probability that a patient will have access to an HLA-matched donor. Despite these nationwide efforts, the success rates of finding fully matched donors are low: in kidney transplantation only 5.5% of patients receiving cadaveric kidneys were matched for 6 of 6 alleles at the HLA-A,-B,-DR loci (*10–12*), and in marrow transplantation a 6/6 match is found less than 65% of the time (Personal Communication, Patricia Coppo, NMDP). Patients who belong to minority racial groups have an even lower probability of receiving matched transplants. For instance, although African-Americans make up 12% of the population, they represent only 2% and 5% of the patients who received HLA-matched unrelated marrow and kidney transplants, respectively. Caucasians, who make up 76% of the population, represent 83% and 90% of the patients who received HLA-matched marrow and kidney transplants, respectively.

Both the UNOS and the NMDP have addressed this problem of inequity by increasing recruitment efforts among minority racial groups. This study addresses the degree of effort necessary to provide equal access for patients in each of the major U.S. racial groups to optimally HLA-matched organ or marrow donors.

MATERIALS AND METHODS

HLA database. The databases utilized for these analyses were provided by the NMDP; they contain the HLA type and racial designation of each patient and donor who, as of April 1995, had either searched for an unrelated donor (potential recipients), or signed up as a volunteer (donors). Patient HLA types presumably represent a true sample of the entire population of patients as they were referred by their physicians for a search based only upon the appropriateness of their diagnosis for marrow transplant, and based upon the unavailability of an appropriate family donor. The donor HLA types presumably represent an unselected subset of HLA types of the indicated racial groups within the U.S.A. Although a substantial number of donors were recruited in drives targeted at specific racial/ethnic groups, there is no reason to presume that this would skew HLA types within the groups. Of the 1,625,159 donors, 1,133,770 were only typed for the HLA-A,-B loci and the remaining 491,389 were typed for HLA-A,-B, and -DR. Those donors whose HLA-A and -B locus antigens were not defined at the level of the 1987 WHO nomenclature (*13*) were excluded from analysis. As the degree of splitting of DR antigens into serologic subtypes was variable, DR antigens were "collapsed" to their DR 1–10 equivalents. Patients and donors who did not have racial designations recorded or were listed as "other" were excluded. Racial designations were self-reported in the following categories: Caucasian, African-American, Asian-American, Hispanic, and Native American. These designations must be considered only approximate, rather than truly genetic, for a myriad of social reasons (*14*).

It was of concern that the HLA-A,-B,-DR typed donors might not represent a true random sample of the overall donor file, as many potential donors were initially only HLA-A,-B typed at the time of recruitment, then were subsequently HLA-DR typed in hopes of matching the specific HLA-A,-B,-DR type of a particular patient. However, when we compared HLA-A and -B antigen frequencies of the HLA-A,-B,-DR typed donors with the HLA-A and -B antigen frequencies of those who were only HLA-A,-B typed, there was no marked difference, implying minimal impact on our study results (data not shown).

All patients and most donors were HLA-typed in laboratories meeting the strict quality control standards of the American Society for Histocompatibility and Immunogenetics.

Calculation of haplotype frequencies. An expectation-maximization (EM) algorithm was used to obtain HLA-A,-B,-DR haplotype frequencies (*15*). The EM algorithm estimates the haplotype frequency iteratively using genotype frequencies, which are updated during each iteration as follows:

$$\Pr(\text{genotype}) = \Pr(\text{genotype}|\text{phenotype})\Pr(\text{phenotype}) \quad (1)$$

where Pr(genotype|phenotype) is calculated using the haplotype frequency estimates from the previous iteration and Pr(phenotype) is the observed phenotype frequency in the data. For example, the conditional probability of the genotype {ABD, abd} given the phenotype {AaBbDd} can be estimated by:

$$\Pr(\{ABD,abd\}|AaBbDd) = 2*h(ABD,abd)/2*|h(ABD)*h(abd) + h(AbD)*h(aBd)+h(ABd)*h(abD)+h(Abd)*h(aBD)|$$

where h(·) is the haplotype frequency. The haplotype frequencies are then computed from the genotype frequencies:

$$h(ABD) = g(ABD,ABD) + (1/2)|g(ABD,abd) + g(ABD,Abd) + g(ABD,aBd) + g(ABD,abD) + g(ABD,ABd) + g(ABD,AbD) + g(ABD,aBD)| \quad (2)$$

where g(·) is the genotype frequency. The initial estimates for the haplotype frequencies are obtained using the square-root method (*16*). The iteration continues until the estimates converge. The EM algorithm leads to the maximum likelihood estimator (*17*). Weir (*18*) provides further discussion of the iterative method and its application to haplotype frequency estimation.

Estimates of phenotype frequencies. The simulation study was conducted in order to estimate the probability of finding a matched donor for donor pools greater than the current size of the registry. The method is described previously by Beatty (*19*). The phenotype frequency of each patient was estimated using the haplotype frequencies derived from the donor database. Any of four different heterozygous genotype combinations of two haplotypes can yield the same phenotype. Thus, a phenotype frequency of {AaBbDd} can be calculated as the sum of the contributing genotype frequencies:

$$\Pr(AaBbDd) = 2*|g(ABD,abd) + g(AbD,aBd) + g(ABd,abD) + g(Abd,aBD)|$$

where g(ABD,abd) represents a genotype frequency of two haplotypes {ABD} and {abd}. Under conditions of Hardy-Weinberg equilibrium, it reduces to:

$$\Pr(AaBbDd) = 2*|h(ABD)*h(abd) + h(AbD)*h(aBd) + h(ABd)*h(abD) + h(Abd)*h(aBD)|$$

* Abbreviations: HLA: human leukocyte antigen NMDP: National Marrow Donor Program; UNOS: United Network for Organ Sharing.

since the probability of a genotype is the product of the two haplotype frequencies.

The multiplication factor "2" accounts for equiprobable genotypes composed of mirror image haplotype combinations, which can be inherited in two ways: h(ABD)*h(abd)=h(abd)*h(ABD). A phenotype frequency of individuals who are homozygous for one or more HLA loci can be obtained similarly with appropriate modifications in the number of contributing genotypes. The phenotype frequency of individuals who are completely homozygous—i.e., Pr(AABBDD)—is defined as h(ABD)*h(ABD) without a multiplication factor.

Estimates of probability of match. The probability of finding at least one 6-antigen HLA-A,-B,-DR matched donor for a patient with a phenotype {AaBbDd} in a registry of n donors is estimated by:

$$\Pr(x>0|n)=1-[1-\Pr(\text{AaBbDd})]^n$$

This probability was computed for each patient in the file, and the mean probability for each racial group was reported.

To assess the expected probability of finding either a 6/6 or a 5/6 match, the same equation is used, except that the phenotype frequency is replaced by the frequency of a 6/6 or 5/6 match. The frequency of phenotypes with either a 5/6 or a 6/6 match for a phenotype {AaBbDd} is defined as:

$$\Pr(\text{5/6 or 6/6 match})=\Pr(\text{xaBbDd})+\Pr(\text{AxBbDd})+\Pr(\text{AaxbDd})+\Pr(\text{AaBxDd})+\Pr(\text{AaBbxd})+\Pr(\text{AaBbDx})-5*\Pr(\text{AaBbDd})$$

where x denotes any allele. For example, $\Pr(\text{xaBbDd})=\sum_i \Pr(\text{iaBbDd})$, where the summation is over all possible A alleles (24 in this case).

RESULTS

All patients who had searched for a donor through the NMDP as of April 1995 were stratified according to one of five racial groups (Caucasian, African-American, Asian-American, Native American, Hispanic). Using a patient/donor matching routine identical to that used by the NMDP, the percentage of full (6/6) HLA-A,-B,-DR matches was determined by searching a virtual "registry" consisting of all 393,132 HLA-A,-B,-DR typed donors of known race who were listed in the NMDP as of April 1995 (excluding those with inadequate HLA-A,-B typing, or those whose race was listed as "other," as noted in the *Materials and Methods* section).

Caucasians had the highest probability of finding a match (78%) compared with the other racial groups: Native Americans (68%), Asian-Americans (60%), Hispanics (62%), and African-Americans (35%). It is known that these racial groups differ among themselves with respect to their distributions of HLA types. Thus, some of this disparity in the probability of finding a match is likely to be a function of the number of Caucasians (274,683), Native Americans (8247), Asian-Americans (29,244), Hispanics (35,512), and African-Americans (45,446) represented in the registry. However, the probability of a patient's finding a 6-antigen match is not a simple function of the proportion of HLA-A,-B,-DR typed individuals of that race in the registry. African-Americans are substantially less likely than are Asian-Americans or Hispanics to find a matched donor despite the fact that they are represented at similar numbers in the registry. We therefore considered the hypothesis that the degree of HLA polymorphism within racial groups might also account for part of the variability in the probability of finding a donor.

One approach to quantitating HLA polymorphism within races is to determine how many new HLA phenotypes are acquired as a function of new donors added for each racial group. For each racial group, we defined a random set of 500 donors derived from our sample as an initial "registry." The proportion of each new random cohort of 500 donors which contributed new HLA phenotypes to the registry was calculated (Fig. 1). Whereas Asian-Americans, Native Americans, and Caucasians have similar curves, African-Americans do not: newly recruited African-Americans are far more likely to have unique phenotypes. For instance, at a registry size of 10,000 donors of a given race, 90% of "new" African-American donors would have new HLA phenotypes, as opposed to 72 or 74% of Asian-Americans or Caucasians, respectively.

The above analysis, which is based on observed phenotypes, only provides insight into the effects of racial HLA polymorphism up to the current size of the registry. In order to model larger hypothetical registry sizes, we took advantage of the observation that HLA-A,-B,-DR antigens are inherited as haplotypes. Given the large number of HLA phenotypes available in the NMDP database for each racial group, it is possible to calculate with reasonable precision HLA-A,-B,-DR haplotype frequencies within each racial group (see the *Material and Methods* section). Haplotype frequencies were estimated for every possible HLA-A,-B,-DR haplotype within each racial group. Using methodology described in the *Materials and Methods* section, these haplotype frequencies were then used to estimate the probability of occurrence of a given HLA-A,-B,-DR phenotype.

The 17,639 patients of known race who have searched for a donor through the NMDP were divided into their respective racial groups; the probability of match for each of these patients' HLA type was then calculated for each of several hypothetical registry sizes. Figure 2 plots the mean probability of finding an HLA-A,-B,-DR match for patients of each racial group from various-sized registries made up solely of donors of their own race. All racial groups have similar shaped curves except for Hispanics and African-Americans, who have lower probabilities at any given donor registry size despite restriction of donors to the recipient's own race.

Might it be possible for patients of poorly represented racial groups to find donors from racial groups which happen to be better represented in the registry? Table 1 displays the mean probability that patients from each race will find a donor in a registry composed exclusively of 500,000 donors of the indicated race. As might be expected, all patient racial

FIGURE 1. Proportion of new HLA phenotypes within each added 500 new "donors" compared with all donors present up to that point.

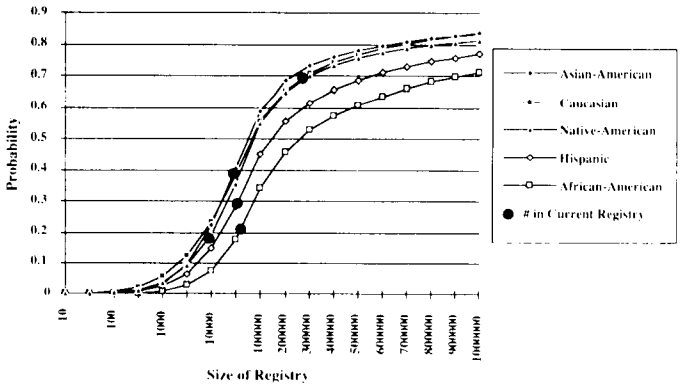

FIGURE 2. Probability of a 6/6 HLA-A,-B,-DR match by race according to size of a modeled registry consisting solely of their own racial group.

TABLE 1. Cross race probabilities: the mean probability that patients of the indicated race will find a 6/6 HLA-A,B,DR match from among a registry of 500,000 donors composed entirely of the indicated race

Patient race	Donor Race				
	Cau	Afr	As	Hisp	Nat
Caucasian	.77	.52	.43	.68	.70
Afr-Am	.18	.61	.08	.26	.20
Asian-Am	.29	.15	.78	.30	.32
Hispanic	.54	.42	.35	.69	.57
Native Am	.61	.49	.53	.71	.76

groups fare best within donor registries of their own race. While 54% of Hispanics are projected to find a matched donor from among 500,000 Caucasian donors, African-Americans are unlikely (18%) to find a donor among Caucasians and very unlikely (8%) to find a donor among Asian-Americans.

To understand why African-Americans appear to have a lower probability of finding a match, three hypotheses were explored. It is possible that inadvertent mistyping of African-American donors and patients artificially decreases the probability of match, because most typing sera available in the United States (including those used to type most donors in the NMDP file) are derived from Caucasians. To test this hypothesis, we randomly introduced "errors" into 5% and 10% of the HLA types of African-American donors, and repeated the same type of analyses as are illustrated in Figure 2. We found that error rates, even of this large magnitude, had a minimal impact on the probability of finding a donor (data not shown).

A second possibility for the increased difficulty that African-Americans have in finding donors might be admixture of Caucasian haplotypes (*20*). African-Americans share 5 of their 20 most common HLA-A,-B,-DR haplotypes with Caucasians, compared with 4 of 20 between Caucasians and Asian-Americans, and 0/20 between Asian-Americans and African-Americans. Thus, some patients defined as "African-American" may have one African-American and one Caucasian haplotype, making it particularly difficult to find an HLA-matched donor, which could add to the diversity of HLA phenotypes among African-Americans. This concern highlights the particular relevance of the term "African-American" as opposed to "black": using the latter designation would imply equivalence between blacks in Africa and blacks living in America (*21*). Modeling studies where "Caucasian" haplotypes were deleted from the African-American haplotype frequency tables led to minimal change in the probabilities (data not shown).

A third possibility derives from consideration of our understanding of the early evolution of the human race. Continental Africans appear to be far more genetically polymorphic and diverse than are other racial groups, perhaps reflecting the origin and lengthy evolution of mankind in Africa prior to exodus (*22, 23*). For instance, when considering mitochondrial DNA data, Africans are far more polymorphic than are any of the other races (*24–26*). With respect to HLA, the cumulative frequency distribution of the top 50 haplotypes in each racial group shows similar curves for Caucasians and Asian-Americans, but a far broader distribution for African-Americans (Fig. 3). The obvious implication is that Caucasians and Asian-Americans have a higher frequency of common haplotypes, thus increasing their chance of finding matched donors within their racial groups. In contrast, African-Americans have more haplotypes; and each one of them is present at lower frequency in the population. Therefore, it is more difficult to find a perfect match even among African-American donors.

As marrow transplantation technology advances, it is possible that some mismatch for HLA may prove feasible (*7, 8*). We therefore calculated the probability that patients within each racial group could find either a complete 6/6 match or a partial 5/6 HLA-A,-B,-DR match. As illustrated in Figure 4, such a "loosening" of HLA matching strategy leads to a substantially higher percentage of patients of all races finding donors, particularly African-American patients.

DISCUSSION

It has been recognized for several years that patients belonging to racial minorities have a substantially lower probability of finding HLA matched organ or marrow donors. This lack of equal opportunity, with the resulting inequality of access to state-of-the-art medical care, is a significant public health and political problem. To date, the proposed solution has been to increase the number of minority marrow and organ donors. However, the results of our study indicate that increasing recruitment efforts can only partially solve the problem.

For Asian-American patients, it appears that it would be

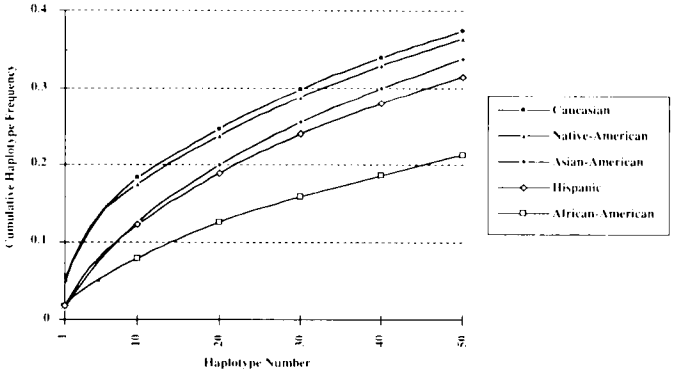

FIGURE 3. Cumulative frequency distribution of the 50 most frequent HLA-A,-B,-DR haplotypes for each racial group.

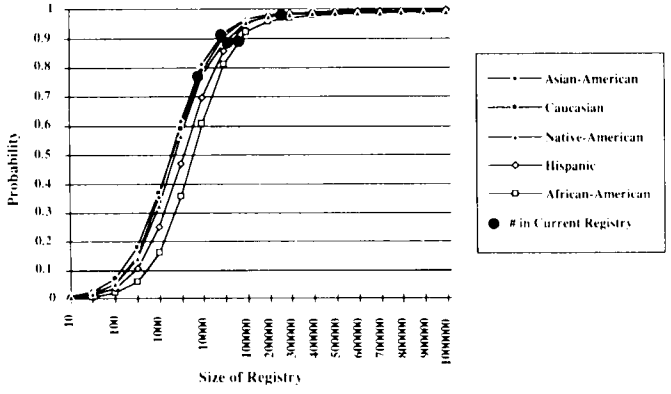

FIGURE 4. Probability of a 5/6 or 6/6 HLA-A,-B,-DR match by race according to size of a modeled registry consisting solely of their own racial group.

necessary to recruit as many Asian-American donors as Caucasian donors to have equal probabilities. However, it is simplistic to consider Asian-Americans en masse, as they are composed of several relatively distinct groups (*23*). For instance, Takahashi et al. published data indicating that the number of Japanese donors needed to effectively serve Japanese patients is relatively small, apparently as a result of limited genetic heterogeneity within that population (*27*). If this observation generalizes to other Asian-American groups (e.g., Korean, Southern Chinese, etc.), it might be useful to target recruitment efforts toward these subsets. Further, collaborative efforts with Asian countries will be particularly important.

With respect to Hispanics, although they are relatively polymorphic for HLA, genetically they may be close to Caucasians. In the 1990 Census, 80% of Hispanics subclassified themselves as Caucasians, 12% as African-Americans, 1% as Native American, the rest as "other" (*28*). Thus, "Hispanic" is more a linguistic definition than a true racial or genetic definition. It therefore appears that the availability of large numbers of Caucasian donors may serve the needs of many Hispanic patients (Table 1).

Although Native Americans clearly represent a defined genetic racial group, among those represented in the NMDP registry there appears to have been considerable admixture of Caucasian HLA haplotypes. However, given the relatively small numbers of Native Americans recruited, it is possible this observation may not be generalizable across all Native American tribes. The NMDP uses a single category for Native Americans, making it difficult to assess how representative the current registry is of all Native Americans in the U.S.

With respect to African-Americans, it would seem necessary to recruit many more African-American donors than either Caucasian donors or Asian-American donors. Such a goal would require recruitment of a substantial percentage of all African-Americans in the United States. For instance, for Caucasian patients to have a 75% chance of an HLA-A,-B,-DR match, 400,000 donors or 0.2% of the 200,000,000 Caucasians in the U.S.A. need to be recruited. For African-American patients to have a 75% probability of a match, 10% (3,000,000 of 30,000,000) of all African-Americans in the United States must be recruited. Thus, even with the recent development of more successful methods of recruiting minority donors, the feasibility of recruiting such a high proportion of the population is problematic.

Despite the potentially enormous effort that would be required to ultimately provide equal probability of match for all races, it should be emphasized that the current focus upon minority recruitment is appropriate, as these efforts are most likely to help the highest proportion of patients in light of the current small numbers of minority donors. For instance, recruiting another 100,000 Caucasian donors would only increase the probability of match for Caucasian patients by 4%. For other racial groups, adding 100,000 donors would add to the probability of match for patients of that particular race by 18% for African-Americans, 24% for Asian-Americans, 20% for Hispanics, and 36% for Native Americans.

The long-range solution to this problem may lie in advances in transplantation technology, which would allow the successful use of partially HLA-mismatched marrow. In renal transplantation an alternative patient/donor matching system based upon similarity for particular amino acids as opposed to specific HLA antigens has been proposed (*29*): this scheme allows for a higher proportion of patients to find acceptable donors. Indeed, the concept of match versus mismatch between two unrelated individuals is indistinct and arbitrary (*30*). Whereas HLA-genotypically identical siblings can be assumed to be virtually identical at the DNA base sequence level throughout their HLA regions, unrelated individuals can be presumed to be matched only to the level of precision of the current typing technology. As this technology advances, it is clear that many putatively "HLA-matched" unrelated individuals differ not only with respect to subtypes of their "classic" HLA-A,-B,-DR antigens, but also often differ for alleles of other loci such as HLA-C, -DQ, and -DP. Furthermore, it is probable that unrelated individuals are more likely than HLA-matched sibling pairs to differ for the minor-histocompatibility antigens (*31*). Thus, any definition of "match" is arbitrary: it is more realistic to determine which are the least dangerous mismatches. Data from Seattle and elsewhere indicate that "minor" degrees of mismatch, while leading to a greater risk of acute graft-versus-host disease, do not necessarily imply a substantially lower long-term survival rate (*8*, *32*). As technology continues to advance, particularly with regard to T lymphocyte manipulation, it may prove possible to loosen the match criteria (*33–35*). If a one-locus mismatch were acceptable, only 30,000 American Caucasians, 30,000 Asian-Americans, and 100,000 African-Americans need to be recruited to have a 90% probability of identifying an acceptable donor.

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